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PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:)	
HIROSHI KASE, ET AL.	:	Examiner: Manu M. Manohar
)	
Application No.: 10/565,239	:	Group Art Unit: 1617
)	
Filed: January 19, 2006	:	Confirmation No. 9168
)	
For: PHARMACEUTICAL	:	
COMPOSITION)	
	:	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. §1.132

Sir:

I, Tomoyuki Kanda, Ph.D., do hereby declare as follows:

1. I attended Toyama Medical and Pharmaceutical University from 1985-1988 and received a Bachelors in Pharmacology in 1988.
2. From 1988-1990, I attended Graduate School of Pharmacology at Osaka University and received a Masters of Science in Pharmacology in 1990. I received my Ph.D. in Pharmacology in 1999.

3. I have been employed by Kyowa Hakko Kogyo Co., Ltd. (now Kyowa Hakko Kirin Co., Ltd.) since 1990. My positions there have been:

1990-2003	Researcher in Neuropharmacology
1993-1995	Visiting Research Fellow of the King's College London, University of London
2003-2008	Senior Researcher, Pharmacological Research Laboratories Pharmaceutical Research Center
2008-present	Senior Scientist, Pharmacological Research Laboratories Research Division

4. I have nearly 25 years experience in pharmacology, and more than 19 years experience conducting pharmacological research and development, including specializing in the field of treating depression.

5. I am familiar with the prosecution and claims of U.S. application No. 10/565,239, including the Examiner's rejection of claims 1, 3, 8 and 9 under 35 U.S.C. §103(a) as being obvious over WO 03/022283 in view of WO 99/12546.

6. I have prepared this Declaration in order to illustrate that use of the present invention unexpectedly achieves vastly superior results over the Examiner's combination of prior art.

7. ICR male mice (20-35g each) were selected for use in an art-accepted animal model of depression¹. The mice were suspended for 6 minutes by adhesive tape, at a site about 2 cm from the tip of their tails, from a bar fixed horizontally

¹ Steru et al., The tail suspension test: a new method for screening antidepressants in mice, *Psychopharmacol.*, Vol. 85, No. 3 (1985) 367-70.

at a height of about 60 cm. Duration of immobility during the last 4 minutes of the 6 minute period was measured (significance test: Student's t test).

8. A representative selective serotonin reuptake inhibitor ("SSRI") and (E)-8-(3,4-dimethoxystyryl)-1,3-diethyl-7-methyl-3,7-dihydro-1H-purine-2,6-dione ("Compound (I)") were separately suspended in distilled water containing 0.5% methyl cellulose. These suspensions were orally administered as described below such that the peak onset of activity of the SSRI overlaps with the peak onset of activity of Compound (I).

9. According to the predetermined time, (i) both suspensions containing the SSRI and Compound (I) were orally administered at 0.1 mL per 10 g body weight to mice. Further, (ii) the suspension containing the SSRI was orally administered to the group, and (iii) a solution of distilled water containing 0.5% methylcellulose without containing any active compounds (the "solvent control group") and (iv) the suspension containing Compound (I) were also administered to groups, each at 0.1 mL per 10 g of mouse body weight.

10. The effects obtained by the foregoing procedures were evaluated according to the following index. The duration of immobility in the solvent control group was assumed to be 100%, and the rate of change (%) of the duration of immobility in each administration group were calculated and compared. The duration of immobility and the rate of change (%) of the duration of immobility in each administration group, is shown in Table 1 and 2 below.

Table 1

Test compound (dose: mg/kg)	Duration of immobility (sec)	Rate of change of duration of immobility to solvent control group (%)
	Mean value \pm Standard error	
Solvent control group	81.3 \pm 13.1	-
Compound (I) (0.04)	70.1 \pm 19.1 *	-14
Paroxetine hydrochloride hydrate (2.50)	79.6 \pm 16.6 *	-2
Compound (I) (0.04) + Paroxetine hydrochloride hydrate (2.50)	31.7 \pm 9.6**	-61

*: Not Significant, **: $p < 0.01$

Table 2


Test compound (dose: mg/kg)	Duration of immobility (sec)	Rate of change of duration of immobility to solvent control group (%)
	Mean value \pm Standard error	
Solvent control group	102.2 \pm 9.1	-
Compound (I) (0.04)	87.9 \pm 14.9 *	-14
Fluoxetine hydrochloride (10.00)	85.7 \pm 18.9 *	-16
Compound (I) (0.04) + Fluoxetine hydrochloride (10.00)	40.5 \pm 14.3**	-60

*: Not Significant, **: $p < 0.01$

11. As seen in Table 1, in the group administered both an SSRI and Compound (I) together, the reduction on the rate of change (%) of the duration of

immobility is enhanced nearly four-fold more (61%) than the expected simple combination of results (2%+16%) obtained by combining the SSRI (2%) and Compound (I) alone (14%). Furthermore, as seen in Table 2, in the group administered both an another SSRI and Compound (I) together, the reduction on the rate of change (%) of the duration of immobility is enhanced two-fold more (60%) than the expected simple combination of results (16%+14%) obtained by combining the SSRI (16%) and Compound (I) alone (14%). In other words, I believe that the use of Compound (I) or a pharmaceutically acceptable salt thereof and an SSRI in combination together enables vastly more effective treatment of depression than would have been expected from the results of using either of these separately.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.



Tomoyuki Kanda, Ph.D.

Date: 25th Jun. 2009